An in vitro stability study of ceftolozane-tazobactam in an elastomeric infusion device for ambulatory care

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Introduction
There is a need for data to support the use of ceftolozane-tazobactam for continuous infusions to be used in outpatient parenteral antimicrobial therapy (OPAT) [1, 2]. In the current study, experimental conditions were established in vitro to assess time, temperature and concentration-dependent stability of ceftolozane-tazobactam encompassing clinically relevant ranges for use as continuous infusion in OPAT [3].

Materials and Methods
Ceftolozane-tazobactam prepared to achieve initial concentrations representing total daily doses for ‘renal’, ‘standard’ and ‘high’ dose schedules (table 1) in LV10 elastomeric infusion devices (Baxter, Old Toongabbie, New South Wales, Australia). Prepared infusates were incubated at body temperature (37°C), room temperature (25°C) or refrigerated at 4°C with samples taken over a 48 to 240 hour period. Samples were assayed for colour, clarity, precipitation visually, subvisible particle detection using a Zetasizer and pH using a pH meter. Concentrations of ceftolozane and tazobactam were separately quantified using a validated ultra-high performance liquid chromatography-photodiode array (PDA) detector method.

Table 1: Dosing Schedules and initial concentrations

<table>
<thead>
<tr>
<th>Dosing Schedule</th>
<th>Total Daily dose</th>
<th>Concentration g/L</th>
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<tbody>
<tr>
<td>C/T</td>
<td>C/T</td>
<td>C/T</td>
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<tr>
<td>Renal</td>
<td>0.45 0.3 0.15</td>
<td>1.25 0.63</td>
</tr>
<tr>
<td>Standard</td>
<td>4.5 3 1.5</td>
<td>12.5 4.25</td>
</tr>
<tr>
<td>High</td>
<td>8 6 3</td>
<td>25 12.5</td>
</tr>
</tbody>
</table>

Results
All samples were free of sub-visible and visible particulate matter and there were no observed changes in clarity or colour. The pH was observed to fall over time under every condition tested although all samples remained within the pH range 5.3–6.2.

Tazobactam showed similar stability to ceftolozane when refrigerated (figure 1) and at room temperature (figure 2) and was clearly more stable at body temperature (figure 2). Ceftolozane met the predefined stability criteria [4] with 97.7% remaining at 24 hours at room temperature for the renal dose, 97.6% for the standard dose and 98.8% for the high dose. Ceftolozane stability was also maintained at 24 hours when incubated at body temperature with 93.0% for the renal, 93.3% for the standard and 93.2% for the high dose.

The relationship between temperature and ceftolozane per cent remaining at 24 hours is shown in figure 3, as data points were seen to cluster, pooled data from the three doses were used to fit an exponential model which gave an estimate for 32°C as 96.2%. There was minimal loss at 4°C with 99.1% ceftolozane remaining at 7 days for renal, 99.9% for standard and 100.0% for high dose preparations (figure 1).

Conclusions
In conclusion, ceftolozane and tazobactam are both stable across a range of clinically relevant temperatures and concentrations in a 240 mL elastomeric infusion device. Ceftolozane–tazobactam is considered suitable for ambulatory care to deliver total daily doses as a continuous infusion.

Figure 1: Scatter plot of ceftolozane (circles) and tazobactam (triangles) concentrations expressed as per cent of baseline mean against time for each of five replicates at renal, standard and high dosing schedules refrigerated at 4°C. Fitted regression lines are plotted with shaded area showing 95% CI. Dotted vertical line identifies the critical time point at 7 days.

Figure 2: Panel of scatter plots showing ceftolozane (circles) and tazobactam (triangles) concentrations expressed as per cent of baseline mean against time for each of five replicates at renal, standard and high dosing schedules incubated at either 25°C representing room temperature or 37°C for body temperature. Fitted regression lines are plotted with shaded area showing 95% CI. Dotted vertical line identifies the critical time point.

Figure 3: Scatter plot of ceftolozane concentrations expressed as per cent of baseline mean against storage temperature at 24 hours. Fitted exponential regression line is plotted with shaded area showing 95% CI. Dotted vertical line identifies the critical temperature of 32°C.

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